REMARKS

Introductory Comments

Reconsideration of the above-identified application in view of the above amendments and arguments set forth is respectfully requested.

Claims 1, 2, 5-10 and 12-16 are pending and under consideration. Claim 4 has been canceled in this amendment. Claims 1 and 6 have been amended as explained below. Claims 17 and 18 are new. Support for these claims can be found in the specification on page 12, line 16 to page 17, line 11. No new matter has been added as a result of these amendments.

Specifically, claim 1 has been amended by reciting "to form complexes" in line 5, in order to provide antecedent support for "the complexes" in line 10. Support for this amendment can be found on page 2, lines 20-23 of the specification. In line 9, "wherein the binding buffer contains no or a low concentration of organic solvent such that" is inserted. Support for this amendment can be found on page 3, lines 17-21 and page 5, lines 20-26 of the specification. In line 13, "step a) allows the nucleic acids to be directly employed in an amplification reaction without exchanging an elution buffer and wherein" is inserted. Support for this amendment can be found on page 3, lines 23-25 of the specification.

Specifically, for claim 6, the Markush grouping language has been inserted in the claim.

Rejection of Claims 1-2, 4-10 and 12-16 Under 35 U.S.C. § 103(a)

Claims 1-2, 4-10 and 12-16 are rejected under 35 U.S.C. § 103(a), as being unpatentable over Uematsu *et al.*, European Patent No. EP 0,757,106 A2 (herein "Uematsu") in view of Kim *et al.*, PCT Publication No. WO 92/18514 (herein "Kim"), and further in view of Chomczynski, U.S. Patent No. 5,934,515.

Specifically, the Examiner asserts that Uematsu discloses a method for isolating a nucleic acid by mixing a metal oxide support, a material containing a

nucleic acid, and a solution for extracting the nucleic acid forming a sample solution, separating the metal oxide support to which the nucleic acid has been bonded from the sample solution, and eluting the nucleic acid from the magnetic carrier to which the nucleic acid has been bonded (Uematsu, page 3, lines 42-45). The Examiner further asserts that Uematsu discloses all of the features of the claims except 1) immobilizing the nucleic acid by forming a bond between the nucleic acid and the metal oxide support, and 2) a binding buffer further comprising an organic solvent, wherein the flashpoint of the binding buffer is greater than 130 degrees Fahrenheit or the use of a reducing agent.

The Examiner contends that Kim teaches bonding nucleic acids directly to a metal oxide material and that Chomczynski teaches using a solution comprising chaotropic agents, a detergent and an organic solvent.

Applicants respectfully traverse this rejection.

Applicants' invention and claims are directed to a method for separating nucleic acids from a test sample in an efficient and simple manner. The concept of the present invention and its benefits are as follows.

It was found that metal oxide particles can be employed to separate nucleic acid from a test sample using no or a low concentration of organic solvent (see the specification, page 3, lines 17-19 and page 5, lines 20-26). With this, Applicants' method for separating nucleic acids from a test sample is more efficient and simple particularly when the separated nucleic acids are employed in an amplification reaction. This is based on the fact that the nucleic acids are eluted from the metal oxide supports using buffers that are completely compatible with amplification reactions (see the specification, page 3, lines 21-23). Thus, the nucleic acids separated from a test sample can be employed in an amplification reaction without the need to exchange the elution buffer with another buffer for an amplification reaction (see the specification, page 3, lines 23-25).

This is accomplished by Applicants' finding that a binding buffer that contains no or a low concentration of an organic solvent which provides a flash point greater than 130 degrees Fahrenheit, is needed. The result is a simplified

method wherein nucleic acids can be purified in an elution buffer employed to dissociate the nucleic acid from a metal oxide support material, and amplification of the nucleic acids can be directly performed with the same elution buffer (see the specification, page 7, lines 19-23).

Thus, Applicants' method uses the direct binding of the nucleic acid to the metal oxide using an ionic interaction between the metal and the phosphate groups of the nucleic acids. This binding is accomplished in a single step process during a lysis-binding step which does not contain organic solvents or contains a very low concentration of organic solvents such that the solution is not flammable (has a flashpoint of greater than 130 degrees Fahrenheit). The nucleic acids are in solution until they bind to the particles. Then, the particles are washed with water to remove contaminants, during which there is no organic solvents needed to keep the nucleic acids bound to the particles because the nucleic acids are bound to the particles via the ionic interaction. Because of this, an elution step is used. The elution step can be performed using a reagent. Examples of reagents that can be used are aqueous buffers containing organic or inorganic phosphate compounds. The phosphate functions as a counter ion for the release of the nucleic acid. Water may also be added during the elution step after the addition of the phosphate containing buffer. The counter ion phosphate has a higher affinity for the metal than the nucleic acid phosphate and thereby displacing the nucleic acid phosphate and allowing it to be eluted. The eluted nucleic acid then can be used directly in an assay.

Uematsu, Kim and Chomcynski, neither individually or collectively disclose or suggest this aspect of the invention. Uematsu does not disclose or suggest a simplified method wherein nucleic acids can be purified in an elution buffer employed to dissociate the nucleic acid from a metal oxide support material, and amplification of the nucleic acids can be directly performed with the same elution buffer. It appears that there are two embodiments where Uematsu mentions amplification. In the first embodiment, Uematsu's "test sample" is the amplified nucleic acid (see Uematsu, page 3, lines 50). In the second embodiment, although Uematsu states that the method includes the step of amplification,

Uematsu does not disclose or suggest amplification directly from the same elution buffer. Uematsu does not disclose or suggest using a buffer that contains no or a low concentration of organic solvent which provides a flash point greater than 130 degrees Fahrenheit.

Additionally, Applicants would like to point the following out to the Examiner with respect to the Uematsu disclosure. Uematsu uses a silica based chemistry which is a hydrophobic chemistry. Uematsu's nucleic acids precipitate on the silica due to high salt and organic solvent concentrations. These nucleic acids that are bound to the silica particles must be washed with alcohol in order to retain them on the particles. They are then released in water. The metal oxides (iron oxides) used by Uematsu is only a support for the silica which allows the silica to be captured with magnetic processes. Thus, the metal oxides used by Uematsu do not play any role in the binding and release of the nucleic acids.

Kim does not cure the deficiencies of Uematsu. On page 10, lines 1-11, Kim generally discloses using an elution buffer comprising Tris, EDTA and phosphate. Kim does not disclose a simplified method wherein nucleic acids can be purified in an elution buffer employed to dissociate the nucleic acid from a metal oxide support material, and amplification of the nucleic acids can be directly performed with the same elution buffer. Additionally, Kim does not disclose or suggest using a buffer that contains no or a low concentration of an organic solvent which provides a flash point greater than 130 degrees Fahrenheit.

Applicants would like to respectfully point out to the Examiner that although Kim uses a method of binding to metal oxide supports, Kim uses lyses and neutralization to "precipitate the desired nucleic acid." Kim does not teach how to bind directly through ionic interaction in a single step lysis procedure.

Finally, Chomczynski does not cure the deficiencies of Uematsu and Kim. Although Chomczynski discloses using a lower amount of organic solvents to precipitate cellular components (Chomczynski, column 3, lines 65-67), Chomczynski does not disclose a simplified method wherein nucleic acids can be purified in an elution buffer that is employed to dissociate the nucleic acid from a

metal oxide support material, and amplification of the nucleic acids can be directly performed with the same elution buffer. Additionally, Chomcyznski does not disclose or suggest using a buffer that contains no or a low concentration of organic solvent which provides a flash point greater than 130 degrees Fahrenheit, especially with an amplification step. It does not appear that Chomcyznski discloses the amplification of nucleic acids at all.

With respect to the mechanism used by Chomczynski, Applicants would like to point out the following. Chomczynski uses a multistep procedure which requires the use of organic solvents to precipitate the nucleic acids via a hydrophobic mechanism. The nucleic acids are kept out of solution by washing the precipitates with alcohol, then drying and then dissolving them. Chomczynski does not disclose or teach binding for ionic interactive methods.

Even assuming *arguendo* that from all of the cited prior art, one can combine together and selectively extract a teaching from each of these prior art, the combined teachings would not result in the claimed method. The claimed method of the present invention provides a simplified method of combining the purification of nucleic acids and directly amplifying these nucleic acids from the same elution buffer. This results in a truly simplified method. The WO publication (Kim) was published more than 10 years ago (1992). If the benefits of Applicants' simplified method are appreciated in the art by others, this method would have been used and published in at least a single document by now.

For all of the reasons set forth, Applicants respectfully request withdraw of the rejection of claims 1-2, 4-10 and 12-16 under 35 U.S.C. § 103(a), as being unpatentable over Uematsu *et al.*, European Patent No. EP 0,757,106 A2 in view of Kim *et al.*, PCT Publication No. WO 92/18514, and further in view of Chomczynski, U.S. Patent No. 5,934,515.

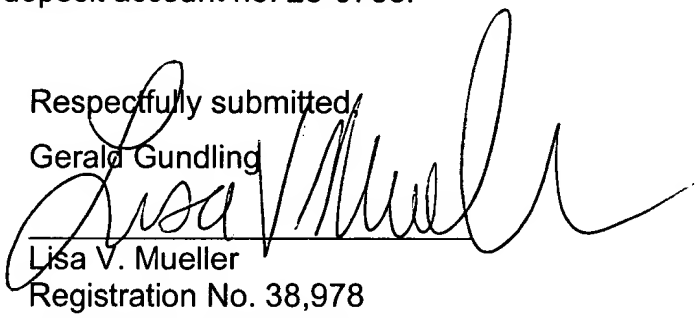
CONCLUSION

Applicants respectfully submit that the claims comply with the requirements of 35 U.S.C. Section 103. Accordingly, a Notice of Allowance is believed in order and is respectfully requested.

Should the Examiner have any questions concerning the above, he is respectfully requested to contact the undersigned at the telephone number listed below. If the Examiner notes any further matters which the Examiner believes may be expedited by a telephone interview, the Examiner is requested to contact the undersigned.

If any additional fees are incurred as a result of the filing of this paper, authorization is given to charge deposit account no. 23-0785.

Respectfully submitted,
Gerald Gundling



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